

Amendments to the Specification (Attorney Docket No. MSB 7272P2)

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- 1) Please replace the paragraph on page 6, paragraph [037] with the following paragraph:

[037] FIG. 10 shows detection of R3P66 by polyclonal antibodies produced in rabbits immunized with R3P66 C-terminus sequence (Ac-CRKQVAACKYLQSIKNKRY-COOH) (SEQ ID NO: 342), using ELISA.

- 2) Please replace the paragraph on page 12, paragraph [061] with the following paragraph:

[061] The invention also provides chimeric or fusion polypeptides. Examples include those polypeptides of this invention described in SEQ ID NOs 18 and 172 which are fusions of the pancreatic targeting sequence "SWCEPGWCR" (SEQ ID NO: 343) (Rajotte D., *et al* (1998) *J Clin Invest* 102:430-437) with SEQ ID NOs 8 and 32, respectively. The targeting sequence is designed to localize the delivery of the polypeptide to the pancreas to minimize potential side effects. The polypeptides of this invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formulation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, Proteins, Structure and Molecular Properties, 2nd ed., T. E. Creighton, W.H. Freeman and

Company, New York (1993); Posttranslational Covalent Modification of Proteins, B. C. Johnson, ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth. Enzymol 182:626-646 (1990); Rattan et al., Ann. N.Y. Acad. Sci. 663:48-62 (1992)).

- 3) Please replace the paragraph on page 14, paragraph [062] with the following paragraph:

[062] The polypeptides of the present invention include the polypeptides of Fig .1, that are SEQ ID NOs: 11 through 14, SEQ ID NO: 18, SEQ ID NOs: 21 through 26, SEQ ID NOs: 32 through 36, SEQ ID NOs: 40 through 53, SEQ ID NOs: 57 through 61, SEQ ID NOs: 63 through 99, SEQ ID NOs: 102 through 119, SEQ ID NOs: 121 through 137, SEQ ID NOs: 139 through 177, SEQ ID NOs: 179, 180, SEQ ID NOs: 183 through 202, SEQ ID NOs: 322 through 341, as well as those sequences having insubstantial variations in sequence from them. An "insubstantial variation" would include any sequence, substitution, or deletion variant that maintains substantially at least one biological function of the polypeptides of this invention, preferably R3 agonist activity, and more preferably selective R3 agonist activity, and most preferably, the insulin secreting activity demonstrated herein. These functional equivalents may preferably include polypeptides which have at least about a 90% identity to the polypeptides of Fig. 1, and more preferably at least a 95% identity to the polypeptides of Fig. 1, and still more preferably at least a 97% identity to the polypeptides of Fig.1, and also include portions of such polypeptides having substantially the same biological activity. However, any polypeptide having insubstantial variation in amino acid sequence from the polypeptides of Fig. 1 that demonstrates functional equivalency as described further herein is included in the description of the present invention.

- 4) Please replace the paragraph on page 37, paragraph [126] with the following paragraph:

[126] Synthesis of the peptide Ac-CRKQVAAKKYLQSIKNKRY-COOH (SEQ ID NO: 342) was performed on an Applied Biosystems 430A peptide synthesizer using fmoc chemistry with HBTU activation of amino acids. The peptide was cleaved using a 84.6% TFA, 4.4% phenol, 4.4% water, 4.4% thioanisol, and 2.2% ethandithiol cocktail. The crude peptide was purified using a C18 reverse phase column with a 0.1%TFA/CH3CN gradient. Evaluation of purity was performed on a PerSeptive V Biosystems Voyager DE Pro MALDI mass spectrometer. The cysteine residue was coupled to KLH using the Pierce Inject Maleimide Activated mCKLH kit and protocol (Pierce , Rockford, IL). Rabbits were immunized using the following polyclonal antiserum immunization schedule:

5) Please replace the paragraph on page 38, paragraph [129] with the following paragraph:

[129] To determine if the antibodies produced in rabbits to the peptide Ac-CRKQVAAKKYLQSIKNKRY-COOH (SEQ ID NO: 342) in accordance with example 17 recognize the peptide R3P66 (SEQ ID NO 72), the enzyme-linked immunoadsorbent assay (ELISA) was performed. When antibodies recognize a peptide, a signal at OD405 is detected. Figure 10 shows that these antibodies recognize R3P66 but do not interact with homologous peptides PACAP-27 or VIP up to 30ug of peptide concentration.